REMARKS

The Office Action dated February 1, 2010, has been received and carefully noted. The above amendments and the following remarks are being submitted as a full and complete response thereto.

Claims 1 and 5-21 are pending in this application. Claims 1, 11, 12, and 15 have been amended herein. Support for the amendments may be found in the specification as originally filed. Applicants submit that no new matter has been added. Applicants respectfully request reconsideration and withdrawal of the outstanding rejections.

Support for Sequence ID No. 1

The Office Action has taken the position that SEQ ID No. 1, as corrected in the claims in the last Amendment, is not supported in the parent international application PCT/IT2005/00088. The Office Action therefore treated claims containing SEQ ID No. 1 as having an effective filing date of July 20, 2007. However, Applicants submit that the 17-mer sequence of the corrected version of SEQ ID No. 1 is supported in the parent application at least on page 5, line 30. *See* WO 2005/080434, excerpt attached.

Rejection under 35 U.S.C. §101

Claims 1 and 11 were rejected under 35 U.S.C. § 101 because the claimed invention was allegedly directed to non-statutory subject matter. The Office Action took the position that the claims include naturally-occurring antibodies and peptides. Applicants submit that claims 1, 11, 12, and 15 have been amended to recite that the

antibodies and peptides are "isolated," as suggested by the Examiner. Accordingly, Applicants respectfully request withdrawal of the objection to claims 1 and 5-21.

Rejections under 35 U.S.C. §102

Claim 11 was rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Fogelman et al. (WO 03/086326).

Claim 11 was rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Wong et al. (*European Journal of Biochemistry*, 1994, Vol. 221, pages 917-925).

Claims 1, 5, 6, 11, and 15-21 were rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Yang et al. (PNAS, 2000, Vol. 97, pages 5907-5912).

Applicants respectfully traverse these rejections.

Applicants submit that claims 1 and 11 are directed to isolated oligoclonal antibodies and immunogenic antigenic epitopes that are selected from sequences ***consisting of*** SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3, and SEQ ID No. 4. The disclosure of Fogelman et al. is directed to identification of immunogenic antigenic epitopes of a human clusterin isoform, Wong et al. is directed to an amino acid sequence for human clusterin, and Yang et al. is directed to a polyclonal antiserum raised by injecting human clusterin into rabbits. Accordingly, Applicants submit that none of these references discloses sequences that ***consist of*** SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3, and/or SEQ ID No. 4. Instead, each of Fogelman et al., Wong et al., and Yang et al. merely disclose a larger sequence corresponding to human clusterin, and do not disclose or suggest isolated oligoclonal antibodies and immunogenic antigenic epitopes.

Accordingly, claims 1, 5, 6, 11, and 15-21 are not anticipated by the disclosures of any of Fogelman et al., Wong et al., and Yang et al., and Applicants respectfully request that this rejection be withdrawn.

Rejections under 35 U.S.C. §103

Claims 1, 5, 11-18, 20, and 21 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over O'Sullivan et al. (*Cell Death and Differentiation*, 2003, Vol. 10, pages 914-927) in view of Wong et al., and Maloy and Coligan ('Selection of Immunogenic Peptides for Antisera Production,' in *Current Protocols in Immunology*, 1991, pages 9.3.1-9.3.5, cited in previous action).

Claims 1, 5-8, 10-18, 20, and 21 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over O'Sullivan et al. in view of Wong et al., and Maloy and Coligan, as applied to claims 1, 5, 11-18, 20, and 21 above, and further in view of Kerr and Thorpe (*Immunochemistry LabFax*, 1994, pages ix-x, 118, 134-135, 142-143, 158-161).

Claims 1, 5, 6, 9-18, 20, and 21 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over O'Sullivan et al. in view of Wong et al., and Maloy and Coligan, as applied to claims 1, 5, 11-18, 20, and 21 above, and further in view of Scheele et al. (U.S. Patent No. 5,663,315).

Applicants respectfully traverse these rejections.

O'Sullivan et al. is cited for disclosing that non-glycosylated, uncleaved isoform of clusterin can be detected in the nuclear fraction of cells undergoing apoptosis after treatment with TNF-alpha or ICI (*see* page 922). During normal synthesis and

secretion, clusterin is translocated to the lumen of the endoplasmic reticulum where it is folded and glycosylated (*see* page 921). Human clusterin has six N-linked glycosylation sites, including alpha-81N (*see* page 914). It is not possible to distinguish whether nascent clusterin was not glycosylated as a result of the TNF-alpha or ICI treatment, or if glycosylated clusterin was deglycosylated prior to retrograde transport to the endoplasmic reticulum and then the nucleus (*see* page 922).

Wong et al. is cited for disclosing the sequences surrounding the six glycosylation sites in human clusterin, and for including SEQ ID No. 2 therein.

Maloy and Coligan is cited for disclosing the selection of a peptide from the C-terminus of a protein as an immunogen (*see* page 9.3.2, under the heading "Selection of a C-Terminal Peptide"). Maloy and Coligan discloses that a peptide having a length of about 15 residues can be used to make an antisera that will react with the native protein (*see* page 9.3.3, under the heading "Selection of the Length of the Peptide").

Kerr and Thorpe is cited for disclosing common methods in immunoassays, and commonly-used antibody labeling tags including fluorochromes (*see* pp. 158-161), isotopes (*see* p. 118), and the enzymes horseradish peroxidase (*see* pp. 134-135) and alkaline phosphatase (*see* pp. 142-143).

Scheele et al. is cited for disclosing common methods for labeling and detecting antibodies, including the use of radioisotopes, fluorophores, horseradish peroxidase, and luciferin (*see* col. 5, lines 12-34).

The Office Action takes the position that it would have been *prima facie* obvious at the time the clamed invention was made to raise antibodies using pairs of peptides representing glycosylation sites of clusterin (as disclosed in Wong et al.), where the

peptide pair was a glycosylated peptide and a non-glycosylated peptide, in order to provide a polyclonal antiserum that binds to the epitope of SEQ ID No. 2 when glycosylated or non-glycosylated. The Office Action further indicated that it would be obvious to use fluorochromes, isotopes, horseradish peroxidase, alkaline phosphatase, or luciferin because they are recognized in the art as useful in labeling antibodies.

Applicants respectfully disagree with the positions taken in the Office Action.

As set forth above with respect to the rejections under 35 U.S.C. § 102, Applicants submit that Wong et al. does not disclose sequences that ***consist of*** SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3, and/or SEQ ID No. 4. Instead, Wong et al. merely discloses sequences surrounding the six glycosylation sites in human clusterin. Applicants submit that it would not be obvious modify the disclosures of O'Sullivan et al. Wong et al., Maloy and Coligan, Kerr and Thorpe, and Scheele et al. to identify the presently-claimed immunogenic antigenic epitopes, or to raise antibodies to them.

Further, Applicants submit that the prior Declaration under 37 C.F.R. § 1.132 of Luigi G. Spagnoli demonstrated that the presently-claimed epitopes provide surprisingly strong sensitivity for detecting clusterin isoforms, and permit evaluation of clusterin increases in early stage cancer patients with higher sensitivity. In view of these unexpected results, Applicants submit that it would not have been obvious for one skilled in the art to modify the teachings of O'Sullivan, Wong et al., Maloy and Coligan, Kerr and Thorpe, and Scheele et al. in order to arrive at the presently-claimed invention.

For at least the above reasons, Applicants respectfully request reconsideration and withdrawal of the rejections of claims 1, 5-8, 9-18, 20, and 21 under 35 U.S.C. §

103(a) over any combination of O'Sullivan, Wong et al., Maloy and Coligan, Kerr and Thorpe, and Scheele et al.

CONCLUSION

Applicants respectfully submit that this application is in condition for allowance and such action is earnestly solicited. If the Examiner believes that anything further is desirable in order to place this application in even better condition for allowance, the Examiner is invited to contact Applicants' undersigned representative at the telephone number listed below to schedule a personal or telephone interview to discuss any remaining issues.

In the event that this paper is not being timely filed, the Applicants respectfully petition for an appropriate extension of time. Any fees for such an extension, together with any additional fees that may be due with respect to this paper, may be charged to Counsel's Deposit Account Number 01-2300, referencing Docket Number 026073-00007.

Respectfully submitted,

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Attachment: Excerpt from WO 2005/080434

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(54) Title: ANTI-CLUSTERIN OLIGOCLONAL ANTIBODIES FOR DIAGNOSIS AND PREDICTION OF THE AGGRESSIVENESS OF TUMOURS, DIAGNOSTIC METHOD AND RELATED KITS

(57) Abstract: The invention concerns anti-clusterin oligoclonal antibodies able to recognize and bind in a selective and specific way antigenic epitopes of clusterin isoforms to be used in tumours diagnosis and in the prediction of their malignancy grade, diagnostic method and related kits.

WO 2005/080434 A1

glycosilated isoforms of cytoplasmic clusterin and to obtain highly specific and selective antibodies for the non-glycosilated nuclear isoform.

It must be pointed out that the commercial anti-clusterin antibodies are not able to identify this nuclear isoforms, because the immunization used for their preparation is done administering the proteins purified from serum, that the authors have recently demonstrated it contains exclusively the glycosilated isoform of the protein.

The authors of the present invention have previously found that in the colorectal cancer the secreted isoform of cytoplasmic clusterin is released in the extra-cellular space and in the lumen of colon, thus an increased level of clusterin also in the stools of the colon carcinoma patients could be expected. Therefore, the dosage of clusterin can be carried out, further than that in peripheral blood, also in the stools of the colorectal cancer patients with a blood-stool cross-shaped test, highly specific for the colon carcinoma. In this manner, the problem of the interference of the increased level of clusterin due to other not tumoural or tumoural diseases (cancer of breast, prostate, testicle, ovary, SNC, haemo-lymphopoietic system) is abolished.

Therefore, it is an object of the present invention oligoclonal antibodies which are able to recognize and to bind in a specific and selective manner the antigenic epitope of at least one isoform of the clusterin, said antigenic epitope being characterised by a length comprised between 10 and 20 amminoacidic residues. The clusterin isoform which is recognized by the anti-clusterin oligoclonal antibodies can be the not-glycosilated nuclear or the glycosilated cytoplasmic one. According to the present invention, these oligoclonal antibodies discriminate between different clusterin isoforms. In particular, the antigenic epitope selected to produce the oligoclonal antibodies against the nuclear not-glycosilated clusterin isoform comprises an amminoacidic sequence selected from the group consisting of:

[QFNWVSRLANTQGEDQK (SEQ ID No.1);] ←

TKLKELPGVCNETMMALWEE (SEQ ID No. 2);

and derivatives thereof obtained by deletion, substitution or addition of one or more amminoacids, which maintain the same